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10/597,787	09/05/2007	Klaus Sommemeyer	021315-08430800	6338

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SCHMIDTMANN, BAHAR	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,787	SOMMEMEYER, KLAUS	
	Examiner	Art Unit	
	BAHAR SCHMIDTMANN	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicant's Amendment and Remarks filed on 02 August 2010 in which claims 17 and 23 were canceled and claims 1-16 and 18-22 were amended to change the scope and breadth of the claims.

Claims 1-16 and 18-22 are pending in the current application and are examined on the merits herein.

Withdrawn Rejections

Applicant's amendment, filed 02 August 2010, with respect to the rejections of claims 1-22 under 35 U.S.C. § 112, second paragraph, for indefiniteness, has been fully considered and is persuasive.

- Claim 17 has been canceled.
- Claims 1, 5, 7, 11, 14, 15, 18 and 19 have been amended to delete the recitation of a broad limitation followed by a narrow limitation. Specifically, the narrow limitations have been deleted.
- Claims 1, 19, 20 and 21 have been amended to delete the recitation "functional", and simply state "amino group", which is understood to contain $-NHR_1R_2$
- The recitation "number average of the mean molecular weight" in claim 12 and "ratio of weight-averaged molecular weight to number average of the mean molecular weight" in claim 13 renders the claims herein indefinite. However, Applicant has stated on the record that "number average of the **mean** molecular weight" is the same thing as "number average of the molecular weight". Thus, it

is clear that the ratio of claim 13 does in fact refer to polydispersity. Although Applicant has clarified this terminology, it is recommended that the claims and specification be amended to recite "number average of the molecular weight".

Thus, the aforementioned rejections are hereby **withdrawn**.

Modified Rejections

The following are new ground(s) or modified rejections necessitated by Applicant's amendment, filed on 02 August 2010, where the limitations in pending claims 1-16 and 18-22 as amended now have been changed, and claim 17 was canceled. Therefore, rejections from the previous Office Action, dated 02 February 2010, have been modified and are listed below.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 16 and 18-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a conjugate from a polynucleotide and a polysaccharide having a reducing sugar, does not reasonably provide enablement for producing a conjugate from a polynucleotide and any and all types of polysaccharides. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1)/(5) *The Nature of the Invention/The Breadth of the Claims:*

The instant invention is drawn to a method for producing a conjugate from any polynucleotide having a functional amino group and any polysaccharide. The instantly claimed invention comprises the steps of "provision of an aldonic acid" of the polysaccharide or polysaccharide derivative.

(2)/(4) *The State of the Prior Art/The Predictability or Unpredictability of the Art:*

Formation of an aldonic acid from a reducing sugar is well known in the art and can be accomplished from a variety of experimental techniques. However, formation of an aldonic acid from any polysaccharide is not known. Polysaccharides and oligosaccharides are composed of monosaccharides glycosylated together. Some oligossacharides and monosaccharides can be chemically modified to an aldonic acid, as in the case of reducing sugars such as maltose, a structural component of starch

(Hecht, *Bioorganic Chemistry: Carbohydrates*, p.41-42, cited in previous Office Action). However, some oligosaccharides and monosaccharides cannot be modified to an aldonic acid as in the case of non-reducing sugars such as sucrose.

Also, carbohydrates have multiple sites of functionality, i.e. multiple hydroxyl groups and/or amine groups that can possibly react with an oligonucleotide. Provision of an aldonic acid ensures reaction at the carboxylic acid moiety of the polysaccharide. However, this provision, which is necessary to ensure the conjugate forms, requires that the polysaccharide have at least one reducing sugar. As a result, forming a conjugate cannot necessarily be formed between a polynucleotide and any polysaccharide. Therefore, forming a conjugate between a polynucleotide having a functional amino group and any polysaccharide is highly unpredictable.

(3) *The Relative Level of Skill in the Art:*

The relative level of skill in the art is high.

(6)/(7)*The Amount of Direction or Guidance Present*/The presence or absence of working examples:

The specification describes formation of conjugates from hydroxyethyl starch (HES) and Spiegelmer of Seq ID No. 1 (p.16-18 and 20-25, examples 1 and 4-14).

(8)*The Quantity of Experimentation Needed:*

Based on the unpredictable nature of the invention and the state of the prior art and the breadth of the claims, one of ordinary skill in the pertinent art would be burdened with undue experimentation study to determine whether any polysaccharide would successfully conjugate to the polynucleotide.

> Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which polysaccharides, if any, would produce the polynucleotide-polysaccharide conjugate with no assurance of success.

Response to Arguments

Applicant's arguments filed 02 August 2010 have been fully considered but they are not persuasive. Applicant has argued that one of skill in the art would readily know what polysaccharide starting materials can be used to make aldonic acid derivatives for use in the claimed invention.

On p.9 of the Remarks, Applicant has admitted that conjugating polysaccharides to polynucleotides is an unpredictable art, and that using EDC for example may not have worked due to possible reactions with the phosphates of polynucleotides. Applicant has also stated that activation of carboxyl groups to form aldonic acid was not even expected. Thus, according to Applicant, the polynucleotide, polysaccharide and activating agent are all unpredictable in the coupling reaction.

The instant claims are not commensurate in scope with the reaction conditions necessary to conjugate the polysaccharide to the polynucleotide. Applicant does not have clear support in the instant specification to show enablement of the full scope of the claims of any polysaccharide conjugating to any polysaccharide using a "carbonate derivative of an alcohol".

The rejection is hereby **maintained**.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 18-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "a carbonate derivative of an alcohol" in claims 1 and 7 renders the claim and its dependent claims 2-16 and 18-22 herein indefinite. The recitation of a "derivative" is not clearly defined in the specification, and therefore does not set forth the metes and bounds of the terms "derivative"

The Merriam-Webster's Online Dictionary defines "derivative" as "a chemical substance related structurally to another substance and theoretically derivable from it" (cited in previous Office Action).

Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to "carbonate derivative of an alcohol"

herein. One of ordinary skill in the art would clearly recognize that a "carbonate derivative of an alcohol" would read on those compounds having any widely varying groups that could be used to substitute the compound. Any significant structural variation to a compound would be reasonably expected to alter its properties; e.g. physical, chemical, physiological effects and functions.

Thus, it is unclear and indefinite as to how the "derivative" herein is encompassed thereby.

Response to Arguments

Applicant's arguments filed 02 August 2010 have been fully considered but they are not persuasive. Applicant has argued that "a carbonate derivative of an alcohol" is used as "an appositive part of a phrase defining a specific entity". The specification does not define what a "carbonate derivative of an alcohol" is; let alone what "derivative" can encompass. Thus, the term is still indefinite and one having ordinary skill in the art would not be able to ascertain the metes and bounds of this entity.

The rejection is hereby **maintained**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sommermeyer et al. (US Pre-Grant Publication 2005/0063943, cited in previous Office Action; English equivalent of WO02/080979, cited in previous Office Action) in view of Wilchek et al. (*Applied Biochemistry and Biotechnology*, vol. 11, 1985, cited in PTO-892) and Cook (WO94/01448, cited in previous Office Action) in further view of Vallazza et al. (*Acta Crystallographica Section D*, cited in previous Office Action).

Sommermeyer et al. teaches hydroxyalkyl starch/active-substance conjugates for drug delivery, whereby the starch can be bonded to the active substance via a linker (abstract). Sommermeyer et al. teaches the reducing end of the substituted or un-substituted starch polysaccharide is oxidized to the carboxylic acid (i.e. aldonic acid), and then converted to an active ester (paragraphs 0025-0026). Sommermeyer et al. teaches the oxidation reaction is performed according to the process disclosed in DE 19628705 (also published as US Patent No. 6,083,909). Sommermeyer et al. teaches forming the conjugate in the presence of dry aprotic polar solvents such as dimethylsulphoxide (column 14, paragraph 0188). Sommermeyer et al. teaches the oxidized hydroxyalkyl starch can be treated with an activator in a molar ratio of 20:1 to 1:20, where a ratio of 6:1 to 1:6 is preferred, to form an ester (column 9, paragraph 0127).

Sommermeyer et al. teaches that N-hydroxysuccinimide carbonate is a known activator when coupling a polymer with an N-terminal amino acid (column 2, paragraph 0008). Sommermeyer et al. teaches a specific embodiment of coupling oxidized

hydroxyethyl starch to DNA using a derivative of N-hydroxysuccinimide as the activator (column 13, example 7). Sommermeyer et al. teaches the amide (type of ester) was dialyzed and lyophilized prior to conjugating it with DNA (column 14, paragraphs 0188-0190). Sommermeyer et al. teaches the active substance can be a nucleic acid, in particular D-DNA, L-DNA, D-RNA, L-RNA, D-nucleic acid or L-nucleic acids (column 3, paragraph 0045). Sommermeyer et al. teaches the average molecular weight of a pharmaceutically active substance conjugated to an oligonucleotide as 32 kDa (column 2, paragraph 0017). Sommermeyer et al. teaches reacting the hydroxyalkyl starch with an active substance having a terminal amino group in addition to a terminal thiol group (claim 79).

Sommermeyer et al. teaches the number average molecular weight (M_n) of hydroxyethyl starch for the 130,000 Dalton polysaccharide is 42,600 Da (column 10, paragraph 0139). This gives a ratio of weight average molecular weight to number average molecular weight as 130,000/42,600 which is equivalent to 3.05. Sommermeyer et al. teaches the number average molecular weight for the 9,800 Da hydroxyethyl starch is 3,695 Daltons. This gives a ratio of weight average molecular weight to number average molecular weight as 9,800/3,695 which is equivalent to 2.65. Sommermeyer et al. teaches the DNA conjugated to hydroxyethyl starch has a molecular weight of 15678 Da and 15094 Da (column 15, paragraph 0199). Sommermeyer et al. teaches the preferred substituted starch is hydroxyethyl starch, having a C_2:C_6 substitution in the range from 2 to 20, a molar degree of substitution degree of 0.1 to 0.8 (column 4, paragraph 0051). Sommermeyer et al. teaches

performing the coupling reaction of oxidized hydroxyethyl starch to DNA at a pH 7.44 (i.e. approximately 8.4), (column 14, paragraphs 189 to 190).

Sommermeyer et al. does not expressly disclose the polynucleotide comprises an amino group (instant claim 1, step b and instant claims 19-22). Sommermeyer et al. does not expressly disclose a ratio of weight-averaged molecular weight to number average molecular weight of approximately 1.05 to 1.20 (instant claim 13).

Wilchek et al. teaches activating a polysaccharide with N,N'-disuccinimidyl carbonate (title and abstract). Wilchek et al. teaches a "ready-made activated column" with the carbonate can be purchased and allows for fixed amount of activation (p.192, first paragraph). Wilchek et al. teaches the N,N'-disuccinimidyl carbonate is stable, commercially available and can be stored for years (p.192, fourth paragraph). Wilchek et al. teaches that the polysaccharide activated with the carbonate can then be reacted with an amino-containing ligand (p.192, third paragraph).

Cook teaches the polysaccharide dextran can be attached to the 5'end of the oligonucleotide via an $-NH_2-(CH_2)_6-$ linker (i.e. 5-aminohexyl), (p.5, second paragraph). Cook teaches the oligonucleotide ester can be produced via the active ester of the pharmaceutically active substrate with the 5'-amino group of the oligonucleotide (p.7, third paragraph). Specifically, Cook teaches reacting a pharmaceutically active substrate with N-hydroxysuccinimide (abbreviated NHS) which is then reacted with the aminohexyl linker that is attached to the 5'-phosphate moiety of the oligonucleotide (p.8, second paragraph). Cook teaches modifying the acid of a sugar to form an active ester which can then be coupled with the amino group of an oligonucleotide to form the amide

conjugate bond (p.10, first paragraph). Cook teaches that polysaccharides such as cyclodextrin, dextrans and starch can be conjugated to the oligonucleotide (p.12, penultimate paragraph). Cook teaches forming the conjugate in the presence of a sodium phosphate buffer to ensure a pH of 8.25 (p.14, first paragraph). Cook teaches modifying a pharmaceutically active agent (such as dextran in example 8) to an active ester via NHS, and then reacting the active ester with the 5'-amino oligonucleotide to give the amide conjugate in the presence of a buffer pH 8.25 (p.25, example 1 and p.8, example 8). Cook et al. teaches that starch has similar or identical carbohydrate monomer units as dextran, therefore the same methods for the conjugation to oligonucleotides can be employed (p.15, last paragraph).

Vallazza et al. teaches aptamers as D-RNA molecules that have high affinity for a wide variety of target molecules (p.1, *Introduction*). Vallazza et al. teaches Spiegelmers as L-RNA mirror images of these molecules which are more resistant to enzymatic degradation, i.e. more stable *in vivo* (p.1, *Introduction*). Vallazza et al. teaches Spiegelmers are pharmacologically viable because they are biophysically similar to aptamers (p.2, third paragraph). Vallazza et al. teaches that Spiegelmers are promising pharmacological targets because their chiral nature ensures they are stable since their corresponding RNases are not found in nature (p.2, third paragraph).

It would have been obvious at the time the invention was made to use N-hydroxysuccinimide carbonate to activate the oxidized starch to an ester and conjugate this to a 5'-aminohexyl group bound to a terminal phosphate of a polynucleotide, without a purification step, wherein the polynucleotide is an aptamers or Spiegelmers; and to

decrease the ratio of weight-averaged molecular weight to number average molecular weight of hydroxyethyl starch to approximately 1.0.

Based on the teachings of the MPEP and KSR mentioned in the previous Office Action, by employing the rationale in (B) simple substitution of one known element for another to obtain predictable results; (G) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention; one having ordinary skill in the art would have been motivated to use N-hydroxysuccinimide carbonate to activate the oxidized starch to an ester and conjugate this to a 5'-aminohexyl group bound to a terminal phosphate of a polynucleotide without a purification step, wherein the polynucleotide is an aptamers or Spiegelmers; and to decrease the ratio of weight-averaged molecular weight to number average molecular weight of hydroxyethyl starch to approximately 1.0.

However, to save time and potential loss of product, one having ordinary skill in the art would also be motivated to withhold an intermediary purification step, and purify after the conjugate has been formed. This method has been demonstrated by Cook et al.

From Sommermeyer et al., one having ordinary skill in the art would have known that oxidized polysaccharides can be activated to an ester using a derivative of an alcohol, such as a derivative of N-hydroxysuccinimide and then conjugated to DNA, i.e. a polynucleotide. Sommermeyer et al. also teaches that the use of N-hydroxysuccinimide carbonate is also a known technique when conjugating to an amino

containing biomolecule. From Wilchek et al., one having ordinary skill in the art would know that the aforementioned N-hydroxysuccinimide carbonate has been used in the art to activate polysaccharides so that they can then be conjugated to an amino containing biomolecule. Wilchek et al. also teaches the carbonate derivative of an alcohol is stable, and commerically available. Thus, one having ordinary skill in the art would have been motivated to substitute the derivative of N-hydroxysuccinimide taught by Sommermeyer et al. with the carbonate derivative of N-hydroxysuccinimide to activate the oxidized hydroxyethyl starch to an ester.

From Cook et al., one having ordinary skill in the art would know that not only can polysaccharides be conjugated to polynucleotides as taught by Sommermeyer et al., but that these polynucleotides can have a 5-aminohexyl bound to a terminal phosphate of the polynucleotide so that the amino group can be used to form an amide bond to a activated polysaccharide ester (via an N-hydroxysuccinimide). Sommermeyer et al. suggested this by teaching the polynucleotide could include a covalently bound linker and that an amino group of the biomolecule could be used to form a conjugate with the polysaccharide.

Furthermore, Sommermeyer et al. teaches the oligonucleotide complex can include D-RNA (i.e. an aptamer) or an L-RNA (i.e. a Spiegelmer). Vallazza et al. teaches that both aptamers and Spiegelmers are pharmaceutically viable and are advantageous in that they have a high affinity for a wide variety of target molecules. One having ordinary skill in the art would therefore be motivated to use aptamers,

especially Spiegelmers since they have the added feature of being more stable to enzymatic degradation.

With respect to polydispersity, it is well known in the art that a polydispersity index of 1 (i.e. wherein the ratio of weight average molecular weight to number average molecular weight) represents a uniformly distributed polymer. Sommerymeyer et al. teaches polysaccharides having a polydispersity of approximately 2.5 to 3.0. These values show that the polysaccharides taught by Sommermeyer et al. are substantially similar in uniformity as those instantly claimed and that a uniform distribution of polysaccharides is desired. Thus, it would have been obvious to decrease the ratio as close to 1 as possible.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teaching of the prior art.

Response to Arguments

Applicant's arguments with respect to claims 1-22 have been considered but are moot in view of the new ground(s) of rejection.

Applicant has argued that neither Cook nor Sommermeyer not teach or suggest an aldonic acid of a polysaccharide, and that Cook does not teach or suggest a carbonate of an alcohol. Because of the currently amended claims which now require a "carbonate derivative of an alcohol", and clarification of the indefiniteness of the term "number average of mean molecular weight", the previous 103 rejection has been modified.

Sommermeyer et al. teaches hydroxyethyl starch was modified according to the process disclosed in DE 19628705 (also published as US Patent No. 6,083,909). It is noted that this method is the same method disclosed in the instant specification for producing aldonic acid from hydroxyethyl starch (see instant specification, p.16, Example 1, last paragraph). Thus, while Sommermeyer et al. does not expressly disclose the reducing sugar of hydroxyethyl starch formed aldonic acid, there is a reasonable expectation that the starch was oxidized to form aldonic acid.

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Sommermeyer et al. also teaches carbonate derivative of an alcohol can be useful for conjugating polysaccharides to amino groups of biomolecules.

Applicant has argued that Valazza et al. relate to aptamers and does not relate to a method of conjugating a particular polysaccharide to a particular polynucleotide.

It should be noted the instant claims are also not drawn to any particular polysaccharide or particular polynuceotide. Valazza et al. teaches that the aptamers and Spiegelmers taught by Sommermeyer et al. are preferable forms of DNA/RNA because of their stability to enzymatic degradation.

Applicant has also argued that EDC was found to be inefficient with polynucleotides. However, the cited art teaches the use of N-hydroxsuccinimide derivatives, including carbonate derivative of N-hydroxysuccinimide as now amended. Hence, the argument is moot.

The rejection is hereby **maintained.**

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. BAHAR SCHMIDTMANN whose telephone number is 571-270-1326. The examiner can normally be reached on Mon-Thurs 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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